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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
SJB:AJH:TR:FP20435		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/AU2004/001333	29 September 2004	30 September 2003

International Patent Classification (IPC) or national classification and IPC

Int. Cl.

A61K 39/00 (2006.01) ***A61P 37/02*** (2006.01)

Applicant

TELETHON INSTITUTE FOR CHILD HEALTH RESEARCH et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      - [ ] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      - [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - [X] Box No. I Basis of the report
   - [ ] Box No. II Priority
   - [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - [ ] Box No. IV Lack of unity of invention
   - [X] Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - [ ] Box No. VI Certain documents cited
   - [ ] Box No. VII Certain defects in the international application
   - [X] Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29 April 2005	20 January 2006
Name and mailing address of the IPEA/AU	Authorized Officer
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/001333

Box No. I Basis of the report

1. With regard to the language, this report is based on:

[X] The international application in the language in which it was filed

[ ] A translation of the international application into , which is the language of a translation furnished for the purposes of:

[ ] international search (under Rules 12.3(a) and 23.1 (b))

[ ] publication of the international application (under Rule 12.4(a))

[ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

[ ] the international application as originally filed/furnished

[X] the description:

pages **1-27, 29-35** as originally filed/furnished
pages* **28-28a** received by this Authority on **18 November 2005** with the letter of **18 November 2005**
pages* received by this Authority on with the letter of

[X] the claims:

pages **37-44** as originally filed/furnished
pages* as amended (together with any statement) under Article 19
pages* **36** received by this Authority on **18 November 2005** with the letter of **18 November 2005**
pages* received by this Authority on with the letter of

[X] the drawings:

pages **1/7-7/7** as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[ ] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages
[ ] the claims, Nos.
[ ] the drawings, sheets/figs
[ ] the sequence listing *(specify)*:
[ ] any table(s) related to the sequence listing *(specify)*:

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

[ ] the description, pages
[ ] the claims, Nos.
[ ] the drawings, sheets/figs
[ ] the sequence listing *(specify)*:
[ ] any table(s) related to the sequence listing *(specify)*:

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

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Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	YES
	Claims 1-51	NO
Inventive step (IS)	Claims	YES
	Claims 1-51	NO
Industrial applicability (IA)	Claims 1-51	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

D1: Castro A.G., et al. "Anti-interleukin 10 receptor monoclonal antibody is an adjuvant for T helper cell type 1 responses to soluble antigen only in the presence of lipopolysaccharide", 2000, J. Exp. Med., vol 192, no. 10, pages 1529-1534

D2: Peng H.J., et al. "B-cell depletion fails to arrogate the induction of oral tolerance of specific Th1 immune responses in mice", 2000, Scand. J. Immunol., vol 51, pages 454-560

D3: Wu X., et al. "Selective suppression of antigen-specific Th2 cells by continuous micro-dose oral tolerance", 1998, Eur. J. Immunol., vol. 28, pages 134-142

D4: Jilek S., et al. "Antigen-independent suppression of the allergic immune response to bee venom phospholipase A2 by DNA vaccination in CBA/J mice", 2001, J. Immunol., vol. 166, pages 3612-3621

D5: Melamed D., et al. "Peripheral tolerance of Th2 lymphocytes induced by continuous feeding of ovalbumin", 1996, Int. Immunol., vol. 8, no. 5, pages 717-724

D6: Kim J.H. and Ohsawa M. "Oral tolerance to ovalbumin in mice as a model for detecting modulators of the immunologic tolerance to a specific antigen", 1995, Biol. Pharm. Bull., vol. 18, no. 6, pages 854-858

D7: von Herrath M.G., et al. "Tolerance induction with agonist peptides recognized by autoaggressive lymphocytes is transient: therapeutic potential for type 1 diabetes is limited and depends on time-point of administration, choice of epitope and adjuvant", 2001, J. Autoimmun., vol. 16, no. 3, pages 193-9

D8: Moreland L.W., et al. "T cell receptor peptide vaccination in rheumatoid arthritis", 1998, Arthritis and Rheumatism, vol. 41, no. 11, pages 1919-1929

D9: WO 2001/052886 A (Alfred Hospital et al.) 26 July 2001

D10: Tobagus I.T., et al. "Adjuvant costimulation during secondary antigen challenge directs qualitative aspects of oral tolerance induction, particularly during neonatal period", 2004, J. Immunol., vol. 172, pages 2274-2285

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 22, 32, 35 and dependent claims are not fully supported by the description. There is only support for the method of treating a disease (cf. claim 22), a method of immunotherapy (cf. claim 32) and a method of treating a Th1 or Th2 disease (cf. claim 35) to be a method of immunotherapy or a method treating a Th1 or Th2 disease wherein the immune response is altered. The inventive concept appears to be that administering antigen in an amount so that the immune response is down regulated, followed by subsequent administration of an immunomodifying agent is able to alter the immune response, for example converting a Th1 cytokine profile in a patient into a Th2 cytokine profile. However as currently drafted the claims are not limited to the inventive concept. For this reason claims 22, 32, 35 are not fully supported by the description.

Claim 35 and dependent claims are not fully supported by the description as they omit the feature that an antigen in immunotherapeutic form is administered so that the immune response is down regulated. The inventive concept appears to be that administering antigen in an amount so that the immune response is down regulated, followed by subsequent administration of an immunomodifying agent is able to alter the immune response, for example converting a Th1 cytokine profile in a patient into a Th2 cytokine profile. However as currently drafted the claims are not limited to the inventive concept. For this reason claims 35 and dependent claims are not fully supported by the description.

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Supplemental Box I

Continuation of V:

D10 was published prior to the international filing date but later than the claimed priority date but which would otherwise be considered to be of particular relevance. This document will not be commented on in this report but may be considered relevant during national phase examination.

D1: This paper describes a range of experiments to investigate the activity of anti-interleukin-10 receptor monoclonal antibody (anti-IL-10R mAb). In particular one of these experiments (page 1531, left column) discloses that mice were primed with soluble ovalbumin ($OVA_{323-399}$) peptide or OVA protein in the presence or absence of IL-10 receptor monoclonal antibody (IL-10R mAb). These mice were then rechallenged with OVA protein in Complete Freunds Adjuvant (CFA). This disclosure describes the two major steps of the claimed methods, that is the administration of an immunotherapeutic antigen (priming with OVA protein) and subsequent administration of the same antigen in immunogenic form (rechallenge with OVA protein in CFA). Using the OVA protein it was shown that a Th1 response could be induced.

D2: Mice were administered OVA for five days (step (i) immunotherapeutic antigen) then administered OVA in CFA (step (ii) immunomodifying agent). This resulted in a suppression of the Th1 immune response.

D3: Transgenic mice carrying the OVA peptide fragment 323-339 were administered OVA for 14 consecutive days to induce oral tolerance (step (i) immunotherapeutic antigen) then administered OVA in alum (step (ii) immunomodifying agent). This resulted in a suppression of the Th2 immune response.

D4: Mice were administered phospholipase A_2 (PLA_2) through DNA vaccination (step (i) immunotherapeutic agent), then administered PLA_2 in alum (step (ii) immunomodifying agent). This resulted in a suppression of the Th2 immune response.

D5: Mice were administered OVA for 20 days to induce oral tolerance (step (i) immunotherapeutic antigen), then administered OVA in CFA or OVA in $Al(OH)_3$ (step (ii) immunomodifying agent). This resulted in the induction of IL-4 secretion and suppression of IFN-γ secretion.

D6: Mice were administered OVA to induce oral tolerance (step (i) immunotherapeutic antigen), then administered OVA in CFA (step (ii) immunomodifying agent).

Novelty and Inventive Step

Claims 1-51 are not novel or inventive in light of the disclosure of each of documents D1 to D6.

The present invention is based on the discovery that the administration of an antigen to an individual suffering from a disease to desensitise the individual to the antigen followed by the administration of the antigen in a different form results in the treatment of the disease.

However, the claims as drafted are not limited to the second administration (or the two administrations) being in a different form. Even if the claims were limited to this feature D2 discloses oral administration of OVA followed by intradermal rechallenge with OVA. D5 and D6 disclose oral administration of OVA to induce oral tolerance followed by i.p administration of OVA in complete Freund's adjuvant.

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Supplemental Box

Continuation of: Supplemental Box I

It is noted that induction of oral tolerance is an immunotherapy for allergic and autoimmune diseases, it contributes to the prevention of allergic response and immune mediated diseases. Therefore tolerance is induced in sensitised individuals.

Each of documents D1 to D6 disclose experimental methods exemplifying the steps of (i) administering an antigen to induce tolerance to the said antigen. Followed by (ii) the subsequent administration of the same antigen to alter the immune response that is switch TH1 cytokine profile to TH2 cytokine profile and vice versa.

The definition of the term "immunomodifying form" added to page 28 is exactly how immunomodifying agent has been used in the citations D7 to D9. An immunomodifying form of the antigen in the citations is producing a therapeutic response.

Therefore claims 31, 35, 36 and 51 are not novel or inventive when compared to D7, D8 or D9. As currently drafted, the disclosures of D7, D8 and D9 fall within the scope of these claims. Claim 31 is a kit to be used to alter the Th1 or Th2 response of an individual and contains Th1 antigens, Th1 or Th2 adjuvants, or combinations thereof and instructions for use. Claims 35 and 36 refer to the use of an immunomodifying agent for the manufacture of a medicament for the treatment of a Th1 or Th2 associated disease, while claim 51 refers to immunomodifying agent per se. D7 describes the use of lymphocytic choriomeningitis in combination with CFA or incomplete Freunds Agent (IFA) which is considered to be the immunomodifying agent, and this combination is used to treat diabetes. D8 discloses the use of TCR peptide antigens in combination with IFA to treat rheumatoid arthritis. While D9 describes a DNA encoding an antigen such as the measles virus H or F protein plus a mucosal adjuvant such as the cholera toxin-ß subunit for the treatment of measles. These disclosures clearly fall within the scope of claims 31, 35, 36 and 51 and therefore these claims lack novelty and inventive step.

Industrial Applicability (IA)

The invention defined in the claims has Industrial Applicability in the field of immunotherapy.

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